Short-Term Morbidity and Clinical Response After a 2-Week Versus 6-Week Interval From Debulking Surgery to Adjuvant Chemotherapy in Epithelial Ovarian Cancer

Mohamad Nasir Shafiee,[1] Azmaniza Baharuddin,[1] Maiza Tusimin,[1] Nirmala Kampan,[1] Arifuddin Djuanna,[2] Ahmad Zailani Hatta Mohd Dali[1]

Abstract

Determining the optimal time interval between debulking surgery to adjuvant chemotherapy is crucial in minimizing morbidity among ovarian cancer patients. A total of 43 operable ovarian cancer cases were analyzed comparing between 2-week and 6-week interval. There were no significant different in short term morbidity between the groups. However the 2-week interval group had a better CA-125 reduction.

Background: The purpose of this study was to determine the effect of time interval between debulking surgery to adjuvant chemotherapy on the short-term morbidity and carcinoma antigen (CA)-125 level. **Patients and Methods:** A total of 43 patients with primary debulking surgery for operable stage epithelial ovarian cancer (stage IB to IIIC) from January 2008 to January 2010 were analyzed prospectively. The participants were randomized into 2 groups. The surgical–chemotherapy interval group 2 (SCI2) (n = 22) received adjuvant chemotherapy (carboplatin and paclitaxel) within 2 weeks after primary debulking surgery and the SCI6 (n = 21) group received the same chemotherapy agents 6 weeks after the primary surgery. A computerized randomization technique was used. **Results:** Participants in the SCI2 group had a better CA-125 reduction after 6 cycles of chemotherapy ($P < .005$) compared with the SCI6 group. The incidence of anemia was more significant in the SCI2 group ($P < .005$) than in the other group. However, there were no significant differences in wound breakdown, neutropenia, thrombocytopenia, and clinical response of chemotherapy between the 2 groups. **Conclusion:** Time interval between primary surgery to the commencement of adjuvant chemotherapy had no significant effect on short-term morbidity, but had an improved effect on biochemical (CA-125) response.

Clinical Ovarian and Other Gynecologic Cancer, Vol. 6, No. 1/2, 25-30
Keywords: CA-125, Chemotherapy, Debulking surgery, Morbidity, Ovarian cancer

Introduction

Advanced epithelial ovarian cancer is the most lethal gynecological cancer. The prognosis corresponds well to the stage of the disease. The International Federation of Gynaecology and Obstetrics Annual Report 2006 postulated the 5-year survival rate of 58.5% for stage IIIa, 39.9% for stage IIIb, 28.7% for stage IIIc, and 16.8% for stage IV disease.[1] Residual disease after initial surgery,[2] tumor grade,[3] and histologic type[4] are the most commonly assessed variables to predict the response rate to chemotherapy and survival outcome. Many other prognostic factors have been described previously, which include age, performance status, and carcinoma antigen (CA)-125 level. DNA ploidy, tumor suppressor genes, oncogenes, and growth factors are relatively new prognostication factors for the disease.[5-7]

Previous studies reported a wide range of time interval from primary surgery to chemotherapy, from 3 to 62 days.[5-10] In animal studies, perioperative chemotherapy and a short surgical–chemotherapy interval resulted in an improved survival outcome.[6-9] Theoretically,

[1]Department of Obstetrics and Gynaecology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia
[2]Department of Obstetrics and Gynaecology, Hasanuddin University, Makassar, Indonesia

Submitted: Mar 25, 2013; Revised: Sep 2, 2013; Accepted: Dec 18, 2014; Epub: Dec 28, 2013

Address for correspondence: Mohamad Nasir Shafiee, MD (UKM), MMed O&G (UKM), MRCOG (UK), Department of Obstetrics and Gynaecology, UKM Medical Centre, 56000 Cheras, Kuala Lumpur, Malaysia
Fax: +60391738946; e-mail contact: mgxmnsh@nottingham.ac.uk

2212-9553/$ - see frontmatter
http://dx.doi.org/10.1016/j.cogc.2013.12.005

tumor cells have greatest potential to grow after surgery, hence supporting early adjuvant chemotherapy administration. Nevertheless, results of some clinical trials have failed to support this theory.[9,10] Conversely, there are sparse data to indicate benefits with delayed administration of adjuvant chemotherapy.[10]

Parallel to the worldwide cancer registry, the number of ovarian carcinoma cases reported in our center is increasing with approximately 40 cases per year, with 80% of the cases being of epithelial origin. The conventional first-line chemotherapy agents for epithelial ovarian cancer are platinum-based with a combination of taxane agent. The first cycle is usually commenced after the histopathological report, which takes 3 to 6 weeks after surgery, depending on urgency.

Therefore, this study was aimed at determining the best time interval for adjuvant chemotherapy after debulking surgery. We considered the biochemical response (CA-125) consistent with short-term morbidity based on the occurrence of bone marrow suppression [11] and wound breakdown. The findings would benefit us in deciding the best time for adjuvant chemotherapy, to improve the outcome and quality of life of ovarian cancer patients.

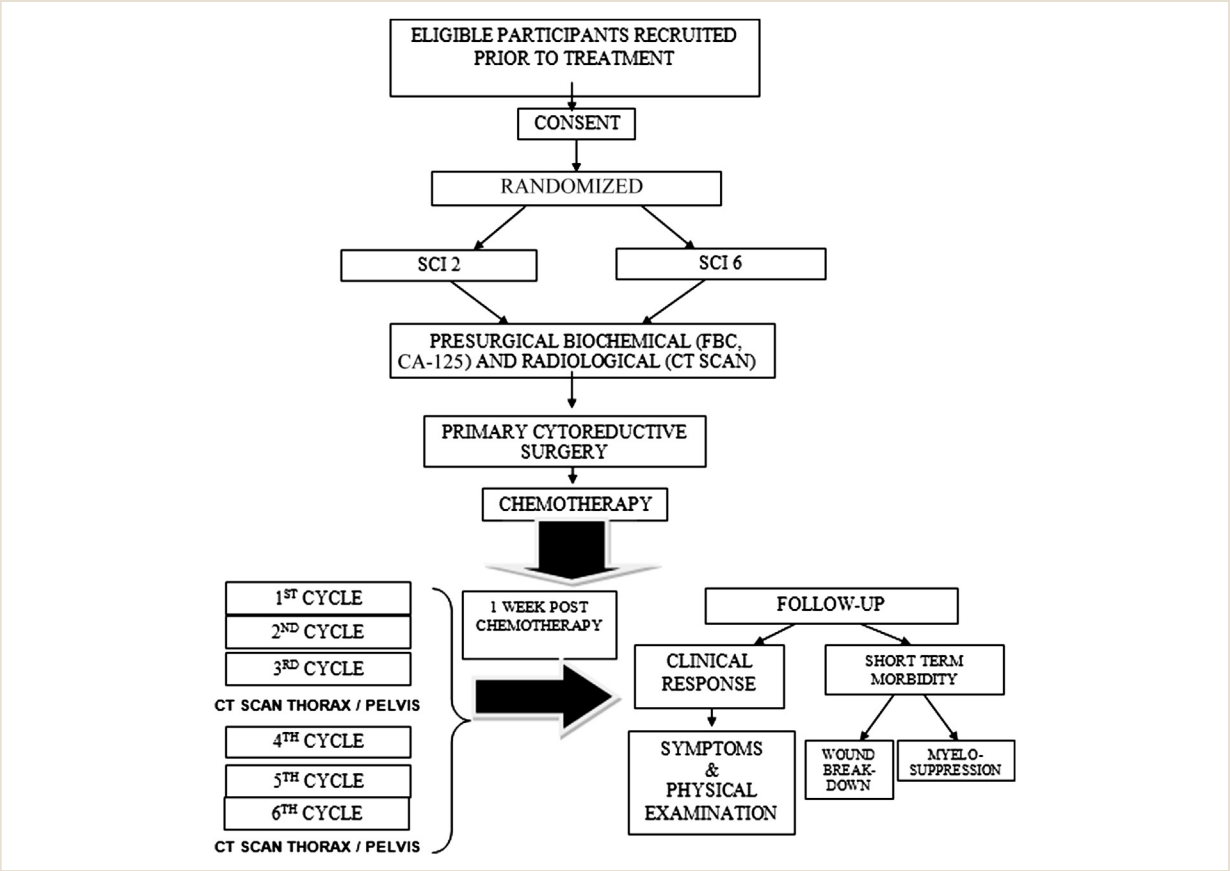
Patients and Methods

A prospective, nonblinded trial conducted in 2 gynecologic oncology centers (Universiti Kebangsaan Malaysia Medical Centre, Malaysia and Hasanuddin Medical Centre, Makassar, Indonesia). We hypothesized a longer interval from surgery to chemotherapy would be associated with less short-term morbidity. Eligibility criteria involved operable stage ovarian cancer, epithelial in origin, participants who required adjuvant chemotherapy after surgery and not contraindicated for carboplatin and taxane agents. University hospital ethics committee approval was obtained before the start of this study.

Eligible participants were recruited after informed consent. Randomization was performed using a computer program and sample size was calculated using StatCal software version 3.0, with 42 samples required for 80% power and P value of $< .05$.

Participants were randomized into a surgical–chemotherapy interval of 2 weeks (SCI2) and surgical–chemotherapy interval of 6 weeks (SCI6) (Fig. 1). They received the first cycle of chemotherapy 2 weeks and 6 weeks after the surgery, respectively. Baseline preoperative investigations included full blood count, CA-125, and computed tomography (CT) scan of the thorax, abdomen, and pelvis performed before staging and debulking surgery by the designated gynecologic oncologists' team. The removed specimen was sent for histopathological confirmation. Adjuvant chemotherapy consisting of 6 cycles of paclitaxel (175 mg/m^2) and carboplatin (area under the curve [AUC] 5) was

Figure 1 Study Flow Chart



Abbreviations: CA = carcinoma antigen; CT = computed tomography; FBC = full blood count; SCI = surgical–chemotherapy interval.

administered with 3 weekly intervals between the cycles as per local protocol.

The outcome measures include short-term morbidity (morbidity occurring within 6 months of chemotherapy which involved wound breakdown and myelosuppression), response to treatment (CA-125 reduction, clinical and imaging [CT scan] evidence of disease), and performance status.[12]

The Eastern Cooperative Group/World Health Organization (WHO) Performance Status Scale defines: 0 = normal activity, no restrictions; 1 = restricted but ambulatory (able to carry out light work); 2 = ambulatory and able to perform self-care but unable to carry out light work for more than 50% of waking hours; 3 = limited self-care and confined to bed or chair more than 50% of waking hours; and 4 = completely disabled/totally confined to bed/might need admission to hospital.[12]

After completion of the sixth cycle of chemotherapy, participants with no evidence of persistence or local recurrence were categorized as complete clinical response.

Data were analyzed using SPSS Version 19.0. The Pearson χ^2 test was used to compare the frequencies of the prognostic factors and chemotherapy in the respective groups (SCI2 and SCI6). The nonparametric correlation between time intervals from primary surgery to the first cycle of chemotherapy was calculated using the Spearman rank correlation coefficient.

Results

A total of 43 participants with epithelial ovarian carcinoma were recruited in this study. The median ages of participants were 50 and 56 years in SCI2 and SCI6, respectively, and not statistically significant ($P = .059$). Most of them were classified according to the American Society of Anesthesiologists as score 1 (25 of 43 participants).

Stage 1C was the highest proportion in SCI2 and SCI6, 11 patients (50%) and 8 patients (38.1%), respectively. However, using Pearson χ^2 test, there was no significant difference between the stage of the cancer in these 2 groups ($P = .097$). Endometroid adenocarcinoma was the most common subtype followed by serous and mucinous adenocarcinoma, but subtype differences were not statistically significant between the 2 groups ($P = .148$). Preoperative CA-125 level was comparable in the SCI2 and SCI6 groups, with 336 U/mL (range, 203-631 U/mL) and 333 U/mL (range, 68.5-704 U/mL), respectively. The findings are summarized in Table 1.

Wound breakdown was not shown to be increased in SCI2 (3 of 22 participants) and SCI6 (2 of 21 participants). There was a significant difference in median total white cell count between the 2 groups after the third and sixth cycle of chemotherapy ($P < .05$). However, only 1 case of neutropenia occurred in the study population, which was not a significant finding. The median platelet counts in the SCI2 group were significantly less compared with the SCI6 group after the third and sixth cycle of chemotherapy ($P < .05$), but the incidence of thrombocytopenia in both groups was not statistically significant (Table 2). After the third cycle of chemotherapy, there was a significant decrease of hemoglobin in the SCI2 group with a median value of 9 g/dL (95% confidence interval [CI], 8.9-9.5) versus 10.5 g/dL (95% CI, 9.8-11.25) in the SCI6 group (Fig. 2).

Table 1 Characteristics of Tumors

Characteristic	SCI2 (n = 22), n (%)	SCI6 (n = 21), n (%)	P
FIGO Classification			
1c	11 (50.0)	8 (38.1)	.097[a]
2a	3 (13.6)	0 (0)	
2b	1 (4.5)	0 (0)	
2c	0 (0)	4 (19)	
3a	4 (18.2)	4 (19)	
3b	1 (4.5)	0 (0)	
3c	2 (9.1)	5 (23.8)	
Histopathology			
Serous	8 (36.4)	7 (33.3)	.148[a]
Mucinous	4 (18.2)	2 (9.5)	
Endometroid	10 (45.5)	9 (42.9)	
Clear-cell	0 (0)	2 (9.5)	
Brenner	0 (0)	1 (4.8)	
Ascites			
Present	18 (81.8)	11 (52)	.065[a]
Not present	4 (18.2)	10 (47.6)	
CA-125 Level (Preoperative)	336 (203,631)	333 (68.5704)	.618[b]

Abbreviations: CA = carcinoma antigen; FIGO = International Federation of Gynaecology and Obstetrics; SCI = surgical–chemotherapy interval.
[a]Pearson χ^2 test.
[b]Mann Whitney *U* Test.

Response to treatment was observed using biochemical markers and performance status. Biochemical response was assessed according to a 50% reduction of serum CA-125 level after completion of the fourth and sixth cycles of chemotherapy.[13] It was shown to be significantly improved in the SCI2 group at the fourth and sixth cycle of chemotherapy ($P < .001$). There was no significant difference in clinical response and rate of recurrence in both groups (Table 3).

Discussion

Advanced stage ovarian cancer has a dismal outcome with an overall 5-year survival rate of approximately 35%.[12] The prognostic factors for ovarian cancer include tumor stage, grade of tumor differentiation, tumor volume, and histological subtypes.[14] A new model to prognosticate early-stage ovarian cancer was designed, which used a combination of age, grade and stage of the tumor, lymphadenectomy, and chemotherapy use. At a cutoff value of 211 for prognostic index, the low- and high-risk groups of recurrence within 5 years were identified.[14]

Various strategies are being implemented to improve clinical outcomes in ovarian cancer. These include a proper referral to the designated gynecologic oncology centers that are equipped with adequate facilities and expertise, adherence to revised guidelines and protocols, and evidence-based recommendations to improve the standard of care.[15] Because most ovarian cancers are chemosensitive, cytoreduction followed by chemotherapy consisting taxane and platinum-based agents represent a standard treatment regime for epithelial ovarian cancers. Carboplatin and paclitaxel thus have

Table 2 Short-Term Morbidity

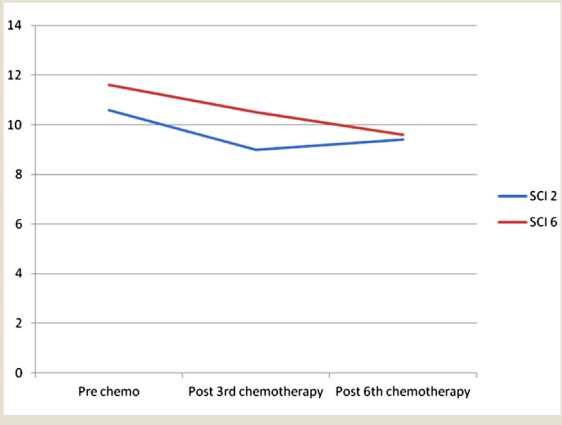
Event	SCI2 (n = 22)	SCI6 (n = 21)	*P*
Wound Breakdown	3 (13.6)	2 (9.5)	1.000[a]
Myelosuppression			
Neutropenia			
WCC third cycle after chemotherapy	7.8 (6.0-8.4)	3.7 (3.25-5.00)	.001[b]
Neutropenia third cycle after chemotherapy	0 (0)	1 (4.8)	.981[a]
WCC sixth cycle after chemotherapy	7.2 (6.6-8.0)	3.7 (3.10-5.70)	<.001[b]
Neutropenia sixth cycle after chemotherapy	0 (0)	0 (0)	—
Thrombocytopenia			
Platelet third cycle after chemotherapy	131 (119-164)	235 (145-283)	.001[b]
Thrombocytopenia third cycle after chemotherapy	3 (13.6)	1 (4.8)	.634[a]
Platelet sixth cycle after chemotherapy	120 (109-138)	193 (133-271)	<.001[b]
Thrombocytopenia sixth cycle after chemotherapy	2 (9.09)	3 (14.2)	.956[a]
Anemia			
Hb before chemotherapy	10.6 (10.0-11.0)	11.6 (10.2-12.3)	.001[c]
Hb third cycle after chemotherapy	9.0 (8.9-9.5)	10.5 (9.8-11.2)	.001[b]
Anemia third cycle after chemotherapy	20 (90.9)	7 (33.3)	<.001[c]
Hb sixth cycle after chemotherapy	9.4 (9.2-10.0)	9.6 (9.0-10.1)	.779[b]
Anaemia sixth cycle after chemotherapy	16 (72.2)	15 (71.4)	.924[c]

Data are presented as n (%) or median (interquartile range).
Abbreviation: Hb = hemoglobin; SCI = surgical—chemotherapy interval; WCC = white cells count.
[a]Continuity correction (Yates correction).
[b]Mann Whitney *U* Test.
[c]Pearson χ^2 test.

widespread acceptance as initial chemotherapy for ovarian cancer because of less risk of nephrotoxicity and neurotoxicity.[16]

Nevertheless, the controversial issue pertaining the optimal duration interval between primary surgery to commencement of chemotherapy is still inconclusive. There are scarce data on effectiveness of adjuvant chemotherapy after primary debulking surgery in animal models.[12,14] A cohort study by Warwick et al, which included 362 patients with advanced disease, showed a poorer outcome in delayed surgery—chemotherapy interval with platinum-based agents. However, the interval was not an independent prognostic factor in multivariate analysis.[15]

Figure 2 Hemoglobin Trend Before Chemotherapy, After the Third Cycle, and After Completed Chemotherapy



Abbreviations: SCI = surgical—chemotherapy interval; SCI 2 = 2-week surgical to chemotherapy interval; SCI 6 = 6-week surgical to chemotherapy interval.

Another study by Flynn et al, which represents The Scottish Gynaecological Cancer Trials Groups 2002, investigated the time interval between primary surgery to chemotherapy (combination of a platinum-based agent and taxane) on the effect of disease-free survival of 472 patients revealed a median interval of 22 days with range of 5 to 113 days. Further analysis found a worse progression-free survival for patient with a shorter interval. However, the drawback of this study was an equivocal selection of bulkier residual disease for early adjuvant chemotherapy.[17]

Gadducci et al investigated the clinical relevance of time interval from primary surgery to chemotherapy in 315 patients with advanced epithelial ovarian cancer who had been given taxane plus platinum-based chemotherapy with intervals of 11 days, 21 days, and 31 days. However, statistical analysis failed to prove any significant differences in complete response and survival rate among the samples.[9]

A total of 43 epithelial ovarian cancer patients were randomized in our study for a 2-week chemotherapy interval (SCI2) with platinum and taxane chemotherapy versus a 6-week interval (SCI6) after primary debulking surgery. The major concern encompassed on short-term morbidity included wound breakdown and myelosuppression (neutropenia, anemia, and thrombocytopenia). There were no significant differences in wound breakdown ($P = 1.000$), neutropenia, and thrombocytopenia in the SCI2 and SCI6 groups after the third and sixth cycles of chemotherapy. However, the baseline level of white cells count in the SCI6 group was

Table 3 Response to Treatment

Type of Response	SCI2 (n = 22), n (%)	SCI6 (n = 21), n (%)	*P* Values
Biochemical Response (Reduction of CA-125 Level)			
After chemotherapy third cycle	4 (18)	3 (14)	1.000[a]
After chemotherapy fourth cycle	21 (95.5)	4 (19.0)	<.001[b]
After chemotherapy sixth cycle	21 (95.5)	9 (42.9)	<.001[b]
Clinical Response (Performance Status)			
After chemotherapy third cycle			
Good response	21 (95.5)	20 (95.2)	1.000[a]
Slow response	1 (4.5)	1 (4.8)	
After chemotherapy sixth cycle			
Good response	19 (86.4)	20 (95.2%)	.634[a]
Slow response	3 (13.6)	1 (4.8)	
Radiological (Rate of Cancer Recurrence)	1 (4.7)	2 (9)	.967[a]

Abbreviations: CA = carcinoma antigen; SCI = surgical–chemotherapy interval.
[a]Continuity correction (Yates correction).
[b]Pearson χ^2 test.

significantly less than in the SCI2 group after the third and sixth cycle of chemotherapy ($P = .01$ vs. $P < .01$). In contrast, the baseline platelet level was improved in the SCI6 group compared with the SCI2 group after the third and sixth cycle of chemotherapy. We postulated a possibility of hematological recovery after blood loss during major surgery. Unfortunately, this parameter was not assessed in this study. The only supported evidence was the greater incidence of anemia in the SCI2 group compared with the SCI6 group after the third cycle of chemotherapy (90.9% vs. 33%, respectively) with a *P* value of .01. Nevertheless, the hemoglobin level improved at the completion of the sixth cycle in the SCI2 group, comparable with the SCI6 group with no significant difference ($P > .05$). A retrospective multicenter study analyzed hemoglobin level before the start of first-line taxane/platinum-based chemotherapy in 315 participants with advanced ovarian cancer found that hemoglobin levels were not an independent prognostic factor for overall survival rate.[9]

Clinical response was assessed using a standard WHO performance status scale, mentioned herein. In this study, we found that there were no significant differences in clinical response and performance status of patients after chemotherapy in the SCI2 group and the SCI6 group ($P = .64$). A previous retrospective study was performed to predict early morbidity at 30 days after debulking surgery in ovarian cancer, particularly aimed at the patient's age, performance status, duration, and extent of surgery. It was reported that WHO performance status was significantly better in the group of patients with an uncomplicated postoperative course ($P = .043$).[18] However, the median age of participants was 64 years with 31% aged older than 70 years. Therefore, it is difficult to conclude whether early chemotherapy (2-week interval) might further complicate the preexisting morbidity.

Biochemical response, assessed by observing the tumor marker trend (CA-125) before and after chemotherapy, was either a 50% reduction of CA-125 in 4 consecutive readings or a 75% reduction of CA-125 in 3 consecutive readings.[13] There was a slight reduction of CA-125 level between the 2 groups after the third cycle of chemotherapy ($P = 1.000$). However, after the completed sixth cycle of chemotherapy, participants in the SCI2 group showed a better reduction in CA-125 level compared with participants in the SCI6 group ($P < .001$). This result showed that early commencement of chemotherapy will improve response to treatment and survival as reported in animal models.[12,14] Even though CA-125 has a poor sensitivity of 35% in monitoring chemotherapy response in ovarian cancer, and it failed to demonstrate any reliable cutoff point value, it is the most commonly used blood parameter. It was statistically found that 20% of the chemotherapy responders will be identified as nonresponders ($P = .025$) in a single study.[19] A more recent analysis determined the efficacy of CA-125 AUC at different stages of epithelial ovarian cancer to prognosticate the overall survival found that the CA-125 level persistently correlated with the disease stage.[20] After the minimum of 3 cycles of chemotherapy (carboplatin and taxol), the median CA-125 was 42.5 (stage I), 58.06 (stage II), 54.6 (stage III), and 149.3 IU/mL (stage IV) ($P = .004$).[20] A level of 99.75 IU/mL CA-125 had a sensitivity of 90.9% with 1.27 as a positive likelihood ratio to predict 5-year survival rate.[20] Radiological response to treatment was assessed by performing a CT scan at the third cycle after chemotherapy and after the completed sixth cycle after chemotherapy. In this study, there were no significant differences in rates of recurrence in both groups with 4.7% in the SCI2 group and 9% in the SCI6 group.

Conclusion

We conclude that using the shorter surgical–chemotherapy interval, the better clinical response is expected without jeopardizing short-term morbidity and patient performance status. Minimization of blood loss at surgery and optimization of hemoglobin level before the start of adjuvant chemotherapy might reduce the incidence of anemia after chemotherapy.

Clinical Practice Points

- The role of adjuvant chemotherapy following debulking surgery in epithelial ovarian cancer is well understood.

- Pertinent issue in determining the best optimal time to commence the chemotherapy is yet to be established.
- Postoperative morbidity and chemotherapy effects are the issues that likely to influence the decision to start on the chemotherapy.
- The 2-week interval between surgery to adjuvant chemotherapy resulted in better CA-125 reduction, without contributing to higher short term morbidity.
- However the recurrence and the overall survival rate are the other issues that need to be looked at in the future research.

Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Heintz AP, Odicino F, Maisonneuve P, et al. Carcinoma of the ovary. FIGO 26th annual report on the results of treatment in gynaecological cancer. *Int J Gynaecol Obstet* 2006; 95(suppl 1):S161-92.
2. Hogberg T, Carstensen J, Simonsen E. Treatment results and prognostic factors in a population-based study of epithelial ovarian cancer. *Gynecol Oncol* 1993; 48: 38-49.
3. Makar AP, Baekelandt M, Tropè CG, et al. The prognostic significance of residual disease, FIGO substage, tumor histology, and grade in patients with FIGO stage III ovarian cancer. *Gynecol Oncol* 1995; 56:175-80.
4. Goff BA, Sainz de la Cuesta R, Muntz HG, et al. Clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy in stage III disease. *Gynecol Oncol* 1996; 60:412-7.
5. Heintz AP, Odicino F, Maisonneuve P, et al. Carcinoma of the ovary. *J Epidemiol Biostat* 2001; 6:107-38.
6. Paulsen T, Kaern J, Kjaerheim K, et al. Symptoms and referral of women with epithelial ovarian tumors. *Int J Gynaecol Obstet* 2005; 88:31-7.
7. Barnholtz-Sloan JS, Schwartz AG, Qureshi F, et al. Ovarian cancer: changes in patterns at diagnosis and relative survival over the last three decades. *Am J Obstet Gynecol* 2003; 189:1120-7.
8. Gadducci A, Sartori E, Landoni F, et al. Relationship between time interval from primary surgery to the start of taxane-plus platinum-based chemotherapy and clinical outcome of patients with advanced epithelial ovarian cancer: results of a multicenter retrospective Italian study. *J Clin Oncol* 2005; 23:751-75.
9. Gadducci A, Sartori E, Landoni F, et al. Relationship between time interval from primary surgery to the start of taxane-plus platinum-based chemotherapy and clinical outcome of patients with advanced epithelial ovarian cancer: results of a multicenter retrospective Italian study. *J Clin Oncol* 2005; 23:751-8.
10. Sorbe B. Prognostic importance of the time interval from surgery to chemotherapy in treatment of ovarian carcinoma. *Int J Gynecol Cancer* 2004; 14:788-93.
11. Rocconi RP, Matthews KS, Kemper MK, Hoskins KE, Barnes MN. Chemotherapy-related myelosuppression as a marker of survival in epithelial ovarian cancer patient. *Gynecol Oncol* 2008; 108:336-41.
12. Oken M. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; 5:649-56.
13. Jim C, Donald B, Roy AJ, et al. Oxford Handbook of Oncology, Oxford, NY. 2002; 23-27.
14. Hyun JP, Eun JN, Sun YR, et al. A new prognostic index model using meta-analysis in early-stage epithelial ovarian cancer. *Gynecol Oncol* 2012; 126:357-63.
15. Warwick J, Kehoe S, Earl H, et al. Long-term follow-up of patients with advanced ovarian cancer treated in randomized clinical trials. *Br J Cancer* 1995; 72:1513-7.
16. Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 2003; 21:3194-200.
17. Flynn PM, Paul J, Cruickshank DJ, Scottish Gynaecological Cancer Trials Group. Does the interval from primary surgery to chemotherapy influence progression-free survival in ovarian cancer? *Gynecol Oncol* 2002; 86:354-7.
18. Gerestein CG, Nieuwenhuyzen-de Boer GM, Eijkemans MJ, et al. Prediction of 30-day morbidity after primary cytoreductive surgery for advanced stage ovarian cancer. *Eur J Cancer* 2010; 46:102-9.
19. Oaknin A, Barretina P, Pérez X, et al. CA-125 response patterns in patients with recurrent ovarian cancer treated with pegylated liposomal doxorubicin (PLD). *Int J Gynecol Cancer* 2010; 20:87-91.
20. Uzunoglu S, Aybatlı A, Kaplan PB, et al. Assessment of CA-125 area under the curve as a prognostic factor in patients with ovarian cancer. *Med Oncol* 2013; 30:447.